THE NEPHROSES *

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The subject assigned to me is very large. With the limited time at my disposal only a brief discussion of its major problems can be undertaken. Fortunately it has received lavish consideration in the past twenty years and the literature is replete with detailed information. While many differences of opinion still exist the fundamentals, upon which our present knowledge is based and which can be traced to the earliest publications on the subject, have suffered no radical change.

When first used, the term nephrosis applied to a group of renal affections in which the dominant pathological change was degeneration of the renal tubules. In this nomenclature were included not only the cases with a degenerative process in the tubules alone, but also those in which the lesion in the tubule was but a part of the diffuse process affecting most or all of the kidney struc- tures. Some of the earlier confusion caused by this terminology arose from the fact that certain cases of diffuse nephritis presented morbid phenomena which corresponded to those found in nephrosis, as well as those peculiar to nephritis.

The term nephrosis as now generally applied represents in reality a compromise between pathologist and clinician. From the pathological standpoint it includes all forms of renal disease with tubular degeneration ranging in degree from cloudy swelling to necrosis and amyloid degeneration; while according to the clinical concept, the term refers to a group of diseases with edema, oliguria, and albuminuria, possessing characteristic biochemical changes in the blood.

The pathologic prototype of nephrosis is the acute nephrosis or that degenerative process of the kidney tubules, which results from certain metallic poisons and bacterial toxins (as in Hg poisoning or diphtheria, etc.).

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The clinical course of these cases is specific and differs widely from that manifested by the group of cases generally designated as chronic nephrosis. Chronic nephrosis in its purest form is a disease which begins insidiously, is of unknown origin and runs a long course characterized by albuminuria, oliguria, edema, without circulatory changes or impairment of renal function, but with certain distinctive changes in the blood.

Despite the difference in the course and character of the acute and the chronic nephroses emphasis is laid principally, by virtue of the term employed, upon the lesions present in the kidneys in both varieties, and yet, it is very questionable whether any link in their pathogenesis actually exists. The direct transition of an acute into a genuine chronic nephrosis is not known to occur.

Notwithstanding the fact that both the acute and chronic types have a common pathologic designation, it is the chronic forms with which we are chiefly concerned. These include three distinct clinico-pathologic varieties: the primary or genuine, or lipoid nephrosis; glomerulonephritis with changes resembling those of genuine nephrosis (the nephrotic component), and amyloid diseases of the kidneys.

Numerous efforts have been made to establish sharp diagnostic criteria for each variety. The urine, the cardiovascular system, the eye grounds, the blood, present on occasions tell-tale evidence pointing to one type of nephrosis or another. However, positive differentiation presents great difficulties, since clinically one variety may closely resemble another. Although the term nephrosis still focuses our attention upon the ultimate pathology in the kidneys, great progress has been made by the realization that other than renal factors are concerned in the clinical manifestations of these diseases. In point of fact, the question has been raised whether or not genuine chronic nephrosis is a renal or a metabolic disorder. A clinical picture resembling that of nephrosis has been recorded in which no albuminuria nor any other evidence of renal involvement is present, the origin of which can be traced

to malnutrition, due to lack of food, or a disturbance in the endogenous metabolism. In other words, failure to assimilate or rebuild the essential body proteins produces a clinical picture similar to that caused by direct loss of protein via the kidneys or any other channel. It is therefore probable that malnutrition is a factor in the protein depletion which occurs in nephrosis. The only difference between the strictly metabolic condition depicted above and that of true nephrosis resides in the albuminuria which accompanies the latter. The albuminuria is the crucial factor in nephrosis, and the entire comprehension of the disease depends upon this fact alone. Some of our difficulty in comprehending this fact arises from our limited ability in discerning cause from effect, a circumstance which leaves open the question as to the true origin of the renal pathology in nephrosis.

In its clinical manifestations and in its chemism, the true or genuine nephrosis is the prototype of all other forms of chronic nephrosis and should be considered first. The etiology of true nephrosis is not known. While the albuminuria is of necessity a renal phenomenon, it is not necessarily, as will be shown later, proof of the existence of renal disease. Some evidence suggests a metabolic derangement as the pathogenic factor. According to this concept the albuminuria is the fundamental disorder and the degeneration of the tubular epithelium of the kidneys, which is characteristic of nephrosis, is an incident in, and not the cause of the disease, while the co-existing inflammatory processes and amyloid deposits may be either independent or incidental.

In the opinion of most pathologists, the kidneys in genuine nephrosis show no evidence of inflammation. Total absence of glomerular lesions is required by some pathologists as a necessary condition for the proper classification of this disease. The tubular degeneration and lipoid infiltration characterizing nephrosis are not of inflammatory origin. However, because of the renal aspects of the disease other pathologists claim it as a degenerative type of nephritis in which the inflammatory

processes subside and the degenerative tubular lesions persist.

The first and foremost manifestation of nephrosis is an intense albuminuria. In acute nephrosis (or that following metallic poisoning or certain bacterial intoxications) the albuminuria, while often intense, is usually of short duration and constitutes merely a sign of the intoxication and no more. In chronic nephrosis, however, the albuminuria is not only intense but is of long duration, lasting months and years. In the light of our present knowledge it stands in immediate relationship to the secondary and characteristic clinical phenomena of all chronic nephroses, namely the edema and the blood changes. The character and duration of these phenomena are often commensurate with the degree and duration of the albuminuria. In the so-called genuine nephrosis, the entire clinical complex appears to be so dependent upon the excretion of albumin in the urine, that the term "Diabetes Albuminuricus" has been suggested by which to designate this condition.

In many instances the albuminuria appears long before any other evidence of disease develops, and its finding may be accidental or casual. The question which requires our first consideration, therefore, is the albuminuria. How is it produced? The proteins present in the urine in albuminuria have been found to be identical with the proteins of the blood. Little if any of the urinary protein is derived from the kidneys. Normally the urine is practically free of protein. The kidneys permit the effete products of metabolism and water to go through but hinder the proteins from leaving the blood stream. However, the passage of protein into the urine occurs in a variety of conditions without concurrent disease of the kidneys. The so-called benign albuminurias belong to this category. They may be of considerable intensity and last for long periods of time, but they are self-limited, and rarely if ever terminate in nephritis.

The passage of protein into the urine is ascribed to a change in the renal filter, conditioned by circulatory changes in the glomeruli. The glomerular origin of the

albuminuria gains some support from the fact that the urinary protein in all albuminurias, whether benign, nephritic or nephrotic (except in amyloid disease) is predominantly serum albumin, namely that fraction of the blood proteins with the smallest molecular configuration.

Face to face with the belief in the glomerular origin of protein excretion stands the fact that the most intense albuminuria occurs in those cases in which the renal tubules, and not the glomeruli, are affected most; whereas, when the glomeruli alone are involved (as in glomerulitis) the least protein is excreted in the urine.

The manner in which the transport of protein from the blood to the urine takes place cannot be regarded as fully determined. The possibility that the renal tubules participate in the excretion of albumin cannot be ignored, particularly as the mechanistic concept of increased glomerular permeability fails to explain the capacity which the kidneys possess, not only of segregating and excreting the blood proteins according to the size of their molecules, but also to eliminate selectively foreign proteins and colloids of the same or higher molecular configuration than those native in the blood. Hemoglobinuria presents a striking example of the selective excretion just alluded to. It is reasonable, therefore, to assume that it is not only the size of the protein or colloid molecule, but a vital inadequacy or a structural change affecting its biologic character which determines the selective elimination of protein from the blood.

The assumption that albuminuria is caused by renal disease is natural, but not conclusive. The fact that the two are commonly associated constitutes an important coincidence, but the exact sequence has not yet been established. What is regarded as cause may only be effect, and vice versa. It is difficult to reconcile the albuminuria of chronic nephrosis with a bizarre and haphazard elimination of protein conditioned by unsubstantiated morphologic change in the glomeruli.

The occurrence of the albuminuria may have another explanation. As stated before, the albumin in the urine

is identical with the protein of the blood. Protein, like cell protoplasm, is plastic in nature and capable of biologic change. The change is qualitative in character, too fine for chemical analysis, but gross enough for the living tissue cells to detect. The life and function of each cell and tissue in the body depend in a large measure on the *biologic accord* existing between the cells and the blood proteins. It is difficult to define this relationship in any other terms. It eludes chemical analysis, but its reality is certain. The blood of one species of animal differs from that of another principally by virtue of the biologic properties of the proteins which it contains. In immunity the capacity of the proteins in the blood, and the protoplasm of the tissue cells for biologic variation and readjustment, is conceded to be of vital importance to the organism. To the best of our knowledge, an immune serum differs from a non-immune serum of the same species of animal in the biologic sense only; chemically the two are indistinguishable. Any change in the blood proteins, however slight, can alter their biologic relation to the tissue cells.

From what we know of the behavior of colloids in general, alterations in pH or a shift in the character or composition of the associated salts or their respective ions may be sufficient to disturb the biologic accord suggested above. Many causes can produce such a change; for example, infections, intoxication, changes in temperature, asphyxia, anoxemia, deficiency of proper food factors, disturbance in acid-base equilibrium, dysfunction of the endocrine glands and parenchymatous organs, etc. If the tissue cells fail to adapt themselves to the new conditions, the blood proteins cease to be supportive or normal in character. They may then be treated as foreign matter and ultimately excreted from the body. By such a mechanism albuminuria becomes a natural and protective process and not a paradox in renal physiology. The morbid manifestations of nephrosis result either from the non-utilization of the proteins or their excretion, or both. It is only in consequence of the excretion of protein from the blood into the urine and its ultimate effect upon the

organism, that the much-discussed varieties of "nephrosis" assume the same secondary clinical manifestations: namely, the blood changes, the edema and the oliguria.

The Blood Changes

The first demonstrable effect of the albuminuria is the change in the content and composition of the blood proteins. Their content decreases, and the fall is proportionate to the duration and intensity of the albuminuria. The output of protein in the urine may range from 5 to 50 grams a day. The total amount of protein in the blood serum of a normal full-grown person weighing 70 kilograms is approximately 200 grams. The albuminuria in nephrosis is of great intensity and may last many weeks or months, so that the protein depletion of the blood may be considerable. Thus while the normal protein content of the blood serum ranges between 6.5 and 8.2 grams per 100 c.c., in the nephroses values below 2 grams per 100 c.c. have been recorded. Coincident with the decrease in the total protein content is the change in the quantitative relations of the individual constituents of the blood. Whereas normally the proportion of the globulin to albumin is approximately as one to two, in these cases the globulin content rises and may constitute the major part of the protein present. Occasionally the inversion reaches extreme proportions, and values have been found in which the globulin constituted as much as 95 per cent of the total serum protein. This remarkable change in the blood cannot be wholly accounted for by a greater elimination of albumin in the urine. Its increase may be absolute as well as relative; and evidence can be adduced that it is of tissue origin. It is certain that the changes just discussed are not due to hydremia or blood dilution.

Various studies indicate that loss of protein from any cause produces a reduction of the protein content of the blood serum. Thus extensive transudation of serum into the serous cavities and into the skin, caused by circulatory failure or static disturbances incidental to the pressure of

neoplasms on blood vessels, hepatic cirrhosis or occlusion of the vena cava (particularly if such fluid accumulations are removed by repeated puncture) is accompanied by a reduction of the protein content of the blood serum.   The experimental removal of blood plasma (plasmapheresis when frequently repeated also causes a diminution of the protein content of the blood.   Rarely is the impoverishment of the blood in serum protein so pronounced, or the inversion of the albumin-globulin ratio of such magnitude, as it is in the true chronic nephrosis.   In purely inflammatory diseases of the kidneys and in any condition in which the anatomic integrity of the kidneys alone is disturbed, even to the point of complete destruction (surgical conditions), such changes are not encountered.

Another effect which accompanies the severe loss of protein from the blood is the accumulation of lipoid material.   A milky appearance of the blood serum due to fatty substances was observed by a number of earlier investigators, in connection with renal affections, but its origin and nature was not determined until recent times. But while the milky appearance of the blood serum is to be observed in some cases, it is absent in others.   Nevertheless an increase in the fatty substances is a fairly constant finding.   One of these fatty substances, the cholesterol, has been studied intensively.   This substance is invariably increased during the active stages of the disease and more particularly when edema is present, and it may attain extraordinary heights.   Values six to eight times the normal are not uncommon.

The cause of this hypercholesterolemia is uncertain. The origin of the cholesterol present normally in the blood has not been fully ascertained.   Undoubtedly some of it is exogenous and some endogenous.   It is subject to fluctuation under a variety of conditions.   In some it appears to be less dependent upon external causes than in others and is definitely associated with metabolic disturbances. Dysfunction of certain endocrine glands, especially that of the thyroid and adrenal, may play a part in determining the cholesterol content of the blood.

The lipoidemia of nephrosis is quite unique. It differs from that of diabetes mellitus. It bears no relation to carbohydrate metabolism and is not associated with either acidosis or ketogenesis. It appears rather to arise directly from impairment of protein metabolism, or protein loss. The lipoid-rich serum of nephrosis differs also in its physical appearance in that free fat is not separated from the serum upon standing or centrifugalization. It appears thus to be in closer physical or chemical contact with the blood proteins, particularly globulin, a circumstance probably of some moment in determining the preferential excretion of albumin in the urine. It behaves differently in a metabolic sense also, since it does not lessen or disappear upon the elimination of fatty foods from the diet. In its general character, the lipoidemia of nephrosis is more like that which arises in endocrine disturbances, particularly in hypothyroidism. It is greater in intensity in nephrosis than in any other known disease.

In seeking an explanation for this phenomenon we find evidence which points to a deficient protein metabolism as the cause of the hypercholesterolemia. This is gleaned from the fact that a certain relationship is frequently observed between the cholesterol content of the blood and the basal metabolism. Although the association is not constant, it may be said in general that conditions which depress the metabolic processes of the body cause an increase in the cholesterol content of the blood, while those which augment metabolism cause a decrease. Thus protein starvation, loss, or non-utilization cause a lipoidemia; while, conversely, protein feeding, pyrexia, and thyroid administration uniformly reduce the lipoidemia. Protein feeding augments metabolism by its specific dynamic action; fever heightens protein catabolism, while thyroid promotes the utilization and catabolism of protein; all these effects are usually accompanied by a fall in the cholesterol content of the blood. These facts, as we shall see later, bear directly on the course and the treatment of the diseases in question.

In a measure the lipoid accumulation in the blood in this disease is proportional to the loss of protein sustained by the blood and to the degree of systemic disturbance which accompanies it. It is perhaps the best measure that we possess of tissue starvation and the metabolic depression. It is superior to the basal metabolism as a measure of deficient protein metabolism and is frequently demonstrable even when the protein content of the blood has not been reduced to a definitely pathologic level.

Among the blood findings there is one other that is regarded as distinctive. That is the non-protein nitrogen. The lack of retention of this constituent in the blood in genuine nephrosis is usually considered as a criterion in the differential diagnosis between this condition and true renal disease. This, however, is misleading because retention of nitrogen in the body takes place in both types of diseases, although in genuine nephrosis it is due to a different cause and is not manifest in the examination of the blood.

The content of the waste products in the blood in the nephroses depends on two factors: the concentrating power of the kidneys, and the water retention of the tissues. In cases of genuine nephrosis the concentrating power of the kidneys is not disturbed but a certain amount of nitrogen waste products is retained in response to the retention of water—which is due to extra-renal factors. Their concentration in the blood remains low because of their diffusion in the water-logged tissues. This is borne out by the fact that when the edema subsides in such cases the waste products dissolved in the edema fluid are transported to the blood and there follows a temporary azotemia or increased nitrogen content of the blood. This results from a difference in the rate of excretion of water and solids by the kidneys, conditioned by the extra-renal factors responsible for the edema. In the uncomplicated cases water and salts are eliminated first, then the nitrogen waste products which lag somewhat behind. Thus an azotemia develops and persists until the accumulated nitrogen waste products of the blood are completely eliminated.

In all other cases in which the kidney filter is affected and the concentrating power decreased, there is a persistent lag in the excretion of nitrogen waste products with the result that the retention of these substances is proportionately greater than the retention of water, and, failing proper dilution, these nitrogen waste products become concentrated alike in the blood and tissue fluids.   This is an important differential point between genuine nephrosis and the nephritides with nephrotic manifestations.

Hematologically, the blood in genuine nephrosis undergoes little or no change from the normal.   In nephritis with nephrotic manifestations and in amyloidosis, the hematology is an expression of the intoxication resulting from renal insufficiency.

The Edema

One of the most striking clinical manifestations of nephrosis is the development of edema.   Its occurrence is intimately associated with a diminished excretion of urine.   Oftentimes it is the first symptom of which the patient complains, and thus leads to the clinical recognition of the malady.

Various explanations have been offered in the past for the occurrence of edema in renal diseases.   Indirectly they all attributed the phenomenon to the retention of water and salts resulting from the inability of the kidneys to eliminate them adequately.   The position of the kidneys in the body economy, however, is such that a change in renal function may be the expression of extraneous influences, and retention of salts and water causing edema may be due to factors other than renal insufficiency.   The fact that the edema in nephrosis is largely of extra-renal origin came to light in 1917, when it was realized for the first time, that the proteins of the blood were definitely concerned with its development.   Some phases of its mechanism appear to be relatively simple.

Between the circulatory medium and the working cells of the body one or more membranes are always interposed. The walls of the blood capillary vessels constitute one such

membrane. All substances that play a part in the nutri-
tion of the cells, as well as the products elaborated by
them so far as they enter the blood stream, must pass
through the walls of the capillaries. The question of how
the fluid exchange through the capillary walls is brought
about hinges ultimately upon two principles, namely, the
intracapillary pressure and the osmotic pressure.

Blood plasma and tissue fluid are identical in every-
thing except the proteins which they contain. Normally
the blood plasma contains more protein than the tissue
fluid. The capillary membranes ordinarily are imperme-
able to the proteins of the blood plasma within the vessel
walls. These plasma proteins or colloids, unable to leave
the capillaries, create an osmotic pressure and by virtue
of their greater content tend to attract and retain fluid
in the blood. The intracapillary pressure on the other
hand works in the reverse way. Accordingly, as the
capillary endothelium is normally impermeable to the
proteins of the blood the movement of the fluid through
the capillary walls depends primarily on the balance
between the intracapillary pressure and the osmotic
pressure of the plasma colloids. An excess of intracapil-
lary pressure would therefore cause fluid to pass towards
the tissues while a converse relation would lead the
movement of fluid into the blood. Otherwise stated, the
direction and the amount of movement of fluid through
the capillary walls is determined principally by the level
of the intracapillary pressures in association with osmotic
factors.

The effect of the two operating forces, however, is differ-
ent. The one, capillary pressure, must cause the passage
of fluid that is of approximately the same composition as
that contained at the source. For example, if transudation
occurs because of increased capillary pressure, the migrat-
ing fluid must be like that of the blood serum or plasma.
This is verified by the composition of effusions encountered
in conditions of static disturbance, such as cardiac decom-
pensation, cirrhosis of the liver, etc. When intracapillary
pressure is lessened (as after hemorrhage) the composition

of the fluid which passes from the tissues into the blood
stream must be like that of the tissue fluid. It is known
that the fluid which passes from the tissues under these
conditions actually contains appreciable amounts of
protein.

On the other hand, the fluid which passes in response
to the osmotic pressure of colloids should be water or an
aqueous solution of salts. Analysis of the edema fluids
in chronic nephrosis show the composition to be one of
salts and water. The protein content is insignificant and
may be derived from the original fluid of the tissue spaces.

Thus we have in these considerations a set of facts which
dove-tail and afford a basis for the comprehension of the
mechanism which leads to the production of edema. It is
recognized on the one hand that the blood serum contains
more protein, i.e. more colloid material, than the tissue
fluid and that by virtue of this predominance it possesses
a greater osmotic pressure than the surrounding tissue
fluid, which is vital in maintaining a balance in the
exchange of fluid between the blood and the tissues.
Speaking figuratively, the osmotic pressure can be com-
pared to the sucking action of a sponge. The examination
of the blood, as already pointed out, in cases of nephrosis
reveals the fact that the protein, i.e. the colloid content,
is very much reduced, and a loss sometimes equivalent to
60 or 70 per cent and more of the total serum protein, often
occurs. In terms of osmosis this loss of protein represents
a decrease in pressure sufficient to disturb the equilibrium
necessary for the normal exchange of fluid between the
blood and the tissues. More precisely, the deficit in the
serum protein causes a fall in the osmotic pressure of the
blood. This disturbance does not only favor the passage
of fluid from the blood to the tissue, but also gives to the
tissues the controlling power to absorb and retain fluid.
Again, as stated before, from the very nature of the force
concerned in the process (that of osmosis) the fluid which
passes from the blood to the tissues must be a solution
of salts. The effusion fluids in the disease under discus-
sion are such solutions.

In discussing the clinical character of genuine nephrosis it was observed above that it is of slow and insidious onset and that the edema is often its earliest symptom. This of course does not signify that the edema marks the beginning of the disease. On the contrary, the presence of edema indicates that the malady is already in an advanced stage. It shows further that the albuminuria has been of sufficient intensity and duration to bring the protein content of the blood to a pathological level.

The exact clinical development of the edema in genuine nephrosis is interesting and worth noting. The function of the kidneys, as is known, may in this disease show slight or no impairment according to the usual tests. But a prolonged and careful study of water metabolism shows that retention of water in the body takes place long before the edema becomes distinguishable. The protein content of the blood serum in such instances shows a moderate reduction below the normal. At a later stage in the disease the edema makes its definite appearance, but is not constant. It may be observed either in the face or back when the patient is in a recumbent position, or in the lower extremities when the patient is up and about. This occurs when the protein content of the blood serum has been reduced to such a level that a critical point in the exchange of fluids between the blood and the tissues has not been reached, but factors of gravity may disturb the balance and thus determine the formation and localization of the edema. It is found at this stage that the blood protein content is still close to 6.0 gms. per 100 c.c. When, however, the protein content of the serum falls to about 5 gms. or lower the edema becomes generalized and is permanent. Posture alone no longer determines its presence or location. In the absence of vascular disturbances, cardiac or hepatic diseases, or inflammation of the kidneys (glomerulo-nephritis), the critical point in respect to the blood serum proteins—the point at which the edema becomes a constant symptom of the disease—is approximately 5 gms. per 100 c.c. It is important to reiterate that the reduction in

the content of the blood serum proteins is due to protein loss and not blood dilution.

Etiology

In the foregoing discussion, the importance of the albuminuria in the clinical evolution of nephrosis was particularly stressed because it is in consequence of the copious excretion of protein from the blood that the three varieties of the chronic nephroses acquire similar clinical characteristics. If, therefore, we assume that the so-called "nephrotic" element (comprising the blood changes, the edema, the oliguria) is in all of them due to one single factor: the albuminuria, the differences as well as the similarities between them cease to be perplexing. Pathologically they have but one feature in common—namely, degeneration of the renal tubules. As indicated, in primary or genuine or lipoid nephrosis, degeneration of the renal tubules is the only alleged pathological change. No other system is affected. There is no hypertension nor any other cardiovascular change. There is no involvement of the eye grounds. Renal function is not disturbed, and pathologic retention of nitrogen in the blood is not demonstrable.

The nephritides with the nephrotic component show all the sequelae of renal inflammation plus those changes in the blood which are directly traceable to the loss of protein occasioned by the albuminuria: namely, the hypoproteinemia, inversion of the protein fractions and the lipoidemia. The edema in these cases may be the composite result of the hypoproteinemia, renal insufficiency and circulatory changes. In amyloidosis, the conditions may be of the same nature as in the nephritides with the nephrotic component—plus certain reactions which are regarded as peculiar to amyloidosis: namely, the predominance of globulin in the urine, the presence of waxy casts —and a positive congo red reaction in the blood. Here again the nephrotic element is conditioned by the protein depletion of the blood resulting from the albuminuria, and not from any pathologic change attributable to amyloidosis.

The basic disturbance in each variety is peculiar unto itself and hence etiologically unrelated. The causes which lead to the development of nephritis or amyloid degeneration of the kidneys are well known—they belong to a separate chapter and need not be considered here. The etiology of genuine nephrosis, however, is still in the realm of the unknown. It occurs most often in young adults and children. The earlier impression that it affects females more often than males, and that it is restricted to the poorer classes should be corrected now.

The individuals particularly prone to this malady are of a peculiar flabby type—some being definitely obese before the disease is discovered. The occurrence of repeated attacks of urticaria marks the early history of some of the cases, and an allergic diathesis must be considered as a possible factor in the etiology of chronic nephrosis.

While in most instances the disease begins insidiously, occasionally it is ushered in by an infection, or it may occur during or after pregnancy, or in the course of some endocrine disturbance—notably hypothyroidism. The transition from hypothyroidism to nephrosis and from nephrosis to myxedema has been observed. While syphilis and tuberculosis are sometimes the cause of chronic nephritis and amyloidosis—they seem to play no part in the etiology of genuine nephrosis. An acute nephrosis in the second stage of syphilis is sometimes encountered—but its transition into a true chronic nephrosis is questionable. The presence of a history of syphilis or a positive serology are no proof of the etiologic relation of lues to genuine nephrosis.

If it is remembered that most cases of chronic nephrosis are discovered at a time when the disease is already well advanced, the factors considered in relation to its etiology may be only incidental and not necessarily generic.

Treatment and Prognosis

In the introductory remarks on the primary or genuine nephrosis, the question was raised as to its real nature.

Is it, or is it not a renal disease? It was intimated that in some respects it bears the earmarks of a metabolic disorder. Upon the correct interpretation of the nature of this disease depend two very important questions: namely, the treatment and the prognosis.

Most true renal diseases which run a chronic course are progressive in character, and in spite of every form of treatment ultimately prove fatal. Upon this basis primary or genuine chronic nephrosis is not a renal disease. Apart from the albuminuria, its resemblance to the clinical condition which results from pure protein starvation is certainly very great. Furthermore experience teaches that although its etiology is uncertain and its duration is usually long, it is amenable to treatment and cure. In essence, genuine nephrosis represents a subversion of protein metabolism. Whatever the cause of the albuminuria may be, the loss of protein substance from the blood, the lipoidemia, the edema and the reduced basal metabolism point to tissue starvation. Hence the treatment to be effective must address itself to these specific indications. Briefly, it resolves itself into three definite propositions:

1. To replace the protein loss of the blood plasma by means of an adequate protein diet. In extreme cases blood transfusion may be necessary.

2. To compel the tissues to utilize the protein and incidentally to reduce the lipoidemia. This, too, is often accomplished by a liberal protein, but fat-poor diet. The administration of thyroid aids in attaining this desideratum.

3. To reestablish normal metabolism. When high protein feeding fails to accomplish this the institution of thyroid is definitely indicated. The main purpose in the use of thyroid is to stimulate protein utilization. It does not aim to replace protein feeding which is fundamental in the treatment of this disease.

The dietary rules are simple, and are amply discussed in the literature. A few remarks on the use of thyroid, however, are in place, particularly because the position

which this agent occupies in relation to chronic nephrosis is very unique.

As stated the purpose in the use of thyroid is solely to accelerate metabolism and thus promote the utilization of protein. The amount of thyroid often necessary to combat the metabolic depression in nephrosis cannot be measured in terms of thyroid hypofunction. It is frequently many times that required in myxedema to reestablish normal metabolic conditions, and the tolerance exhibited by patients with nephrosis for thyroid substance or its active principle thyroxin is quite extraordinary. Details of procedure in its use are recorded in the literature and need not be considered here. Suffice it to say, that thyroid is used only as an adjunct to high protein feeding. Symptoms of intoxication from the use of thyroid are rather exceptional—and when they do occur, are usually temporary and of mild degree.

The symptomatology of genuine nephrosis is so closely interwoven with its biochemistry that whatever modifies its chemism in the right direction, relieves its symptoms and improves the condition. Thus by virtue of a common attribute, stimulation of protein metabolism, beneficial results may follow high protein feeding, thyroid administration and occasionally fever. A bout of fever sometimes marks the turning point towards recovery in a specially refractory case. The use of diuretics for the relief of the edema is occasionally necessary. Amongst those used, urea, calcium and the ammonium salts are preferable. While the mercurial diuretics yield the most dramatic effects, the results are ultimately deleterious and their frequent use is undesirable.

Relief of symptoms and improvement alone are not the sole objects of treatment in genuine nephrosis. Experience teaches that in the absence of uncontrollable and hopeless complications, they are susceptible of complete cure when therapy is intelligently and persistently applied. This may require months or years to accomplish.

The presence of complications alters the outlook and often necessitates modification of the therapeutic pro-

cedures. The commonest accident is infection in which the pneumococcus is the chief offender. The biochemical changes which take place in nephrosis seem to render the conditions particularly favorable for the invasion and multiplication of this micro-organism. The seat of infection is variable: sinusitis, otitis media with and without mastoiditis, pneumonia, erysipelas and thrombophlebitis of the extremities have been observed; but the peritoneal cavity is most often affected. While such infections are of grave portent, they are not necessarily fatal.

Infections in other localities run a course which is not unlike that encountered in other conditions. The outcome depends on the severity of the infection. Occasionally the effect of an infection is rather favorable. As pointed out before, the influence of the associated pyrexia upon the general metabolism is such as to accelerate protein utilization, which high protein feeding and thyroid administration sometimes fail to accomplish. This suggests the possibility that other pyrogenic substances may be of service to initiate the metabolic changes desired in this condition. This, however, is a problem for the future.

In glomerulonephritis with the nephrotic component the treatment is complex and largely symptomatic. On the one hand efforts must be made to replenish the blood protein; on the other, a rising azotemia must often be combatted. Under these circumstances the azotemia should receive first consideration and a low protein diet must be fed until the accumulation of waste products in the blood is adequately overcome. The presence of edema under the circumstances mentioned serves as an aid in overcoming the toxic effects of the azotemia. Removal of fluid accumulated under the skin or in the serous cavities is sometimes desirable and puncture and drainage may be resorted to. When the azotemia is reduced, the protein intake may be increased to a point which is in keeping with the requirements of the body and the functional capacity of the kidneys. However, the progress of the disease is rarely permanently affected by the treatment.

Other symptoms arising from a complicating nephritis are treated in the usual manner, and, according to indications.

Genuine nephrosis, as stated before, is not accompanied by changes in the cardiovascular system. Consequently if elevation of blood pressure occurs it should be regarded with suspicion. Glomerular involvement may be in the course of development.

There is one other group of cases which require special attention, and in which two distinct sets of therapeutic indications exist. The ultimate outcome of these cases depends on the order in which the indications are met. I refer here to the cases of genuine nephrosis with a history of syphilis or in which a positive Wassermann reaction is obtained. In some quarters syphilis is regarded as a cause of genuine or lipoid nephrosis. However, this contention lacks confirmation. Anti-luetic measures are ineffectual in the treatment of genuine chronic nephrosis.

The development of nephritis in the course of a genuine nephrosis which progresses to fibrosis and contraction of the kidneys modifies the course of the disease in a very interesting and enlightening manner. The clinical manifestations which have been described as being "nephrotic" in character (that is the intense albuminuria, the reduction in the total blood serum protein, the inversion of the albumin-globulin ratio, the lipoidemia, the edema, and the oliguria) all retrogress. The albuminuria recedes, and in consequence of this the blood proteins are gradually conserved. Following the conservation of the blood proteins, the inversion of the albumin-globulin ratio also recedes and ultimately assumes approximately normal values. The lipoidemia also follows suit and is gradually reduced to a normal or subnormal level. Polyuria replaces the oliguria and the edema subsides. This course of events constitutes a striking illustration of the interdependence of the clinical phenomena in the nephroses and the albuminuria.

Summary

To summarize: Unlike chronic glomerulonephritis and amyloidosis which are progressive, primary or genuine

lipoid nephrosis is a curable disease. With a quarter of
a century behind it, it deserves consideration as a clinical
entity not only by virtue of its special clinical character-
istics but because of the end results attained. To illustrate:
ten of a series of cured cases of genuine chronic nephrosis
are presented for your consideration. These were selected
especially because they indicate the curability of the
disease and other points of interest considered in the
discussion.

Case 1: J. J. Age 23. Admitted to Mt. Sinai Hospital
on November 10, 1915, as a case of glomerulonephritis
following a throat infection. Subsequent course and
findings proved this to be a case of chronic nephrosis.
Under the customary treatment the patient grew progres-
sively worse. On February 9, 1916, lapsed into a coma
and had several convulsions. No azotemia. Was given
four transfusions of blood. Recovered consciousness.
High protein feeding instituted. Improvement progressive
from that time on. Discharged from hospital April 2,
1916. Free of edema but with the albuminuria persisting.
Total duration of treatment thirteen months. Complete
recovery. Was drafted into the army in 1918. Admitted
to life insurance with normal premiums on three occasions
since then. Last insurance one year ago. Total survival
22 years. In perfect health to date.

Condition ushered in by acute infection—onset similar
to glomerulonephritis.

Case 2: L. S. Age 32. Admitted to Mt. Sinai Hospital
November 2, 1917. Edema of the lower extremities, noted
in the eighth month of the third pregnancy. First two
pregnancies normal. Edema subsided on rest in bed.
Three weeks after parturition generalized edema devel-
oped. Albuminuria observed for the first time. In spite
of customary treatment the edema was progressive, raising
the weight from 130 to 208 pounds. Clinical findings
typical of chronic nephrosis. Following institution of
high protein feeding progressive improvement. Discharged
from hospital April 21, 1918, free of edema. Weight 129½

pounds. Albuminuria persisting.   On June 16, 1918, albu-
minuria disappeared completely.   Patient remained well
since then with no vestige of original disease.   At present
entering climacterium.   Slight rise in blood pressure
without renal involvement.   Survival to date 19 years.

Condition developed during pregnancy.

Case 3:   S. L.   Age 22.   Inmate of several hospitals
prior to coming under observation on February 6, 1918.
No etiology other than that of hypothyroidism.   Clinical
findings that of chronic nephrosis.   Under treatment with
high protein diet and thyroid for nine months with a
complete recovery.   In perfect health to date.   Survival
19 years.

Condition associated with hypothyroidism.

Case 4:   M. Z.   Age 30.   Case of chronic nephrosis
admitted to Mt. Sinai Hospital in 1919.   Case complicated
by positive luetic serology.   Condition aggravated by
anti-luetic treatment.   Discontinued.   Put on a high pro-
tein diet.   This therapy was maintained for three years
with complete recovery.   Survival 17 years.   Has not been
ill since, although constantly exposed to the elements
because of occupation.

Condition associated with luetic serology which has no
etiologic relationship.

Case 5:   H. B.   Age 12½ (nephew of case 3).   Came
under observation in November, 1925.   Diagnosis: chronic
nephrosis.   Course complicated by an intercurrent acute
hemorrhagic   nephritis.   Hematuria   persisted   for   six
weeks.   Except for the latter interval, patient was on a
high protein diet and thyroid for two years with complete
recovery.   In 1936 ill with septic sore throat.   Chills and
high fever up to 104.   This lasted for two and a half weeks.
No recurrence of any renal symptoms and signs.   Survival
12 years.   In perfect health to date.

Acute hemorrhagic nephritis in the course of a chronic
nephrosis.

Case 6: *B. A.* Age 4½. Came under observation for chronic nephrosis in December, 1926. Treated with high protein diet and thyroid (the terminal albuminuria was of lordotic origin). Complete recovery after four years. Had two attacks of broncho-pneumonia and frequent upper respiratory infections in the interim. Since recovery had mumps, scarlet fever and a third attack of broncho-pneumonia. No renal complications or sequelae. In perfect health to date. Survival 11 years.

Condition associated with two intercurrent attacks of broncho-pneumonia, mumps, scarlet fever and a third attack of broncho-pneumonia. Without sequelae.

Case 7: *C. A. B.* Age 10. Came under observation in March, 1925. Alleged to be a case of chronic glomerulo-nephritis following otitis media. Subsequent course that of nephrosis with evidence of hypothyroidism. Was on a high protein diet and thyroid for three years with complete recovery. In July, 1934, cervical adenitis with high temperature followed by suppuration requiring surgery. Uneventful recovery. In 1936 herniotomy. Uneventful recovery. Completely well to date. Survival 12 years.

Condition ushered in with an acute infection—onset similar to glomerulonephritis. Suppurative adenitis subsequently without renal sequelae.

Case 8: *C. T.* Age 19. Admitted to Beth Israel Hospital January, 1931. Antecedent history of diphtheria at the age of three, and severe attacks of giant urticaria for two and a half years prior to present illness. Clinical appearance and course that of nephrosis with evidence of hypothyroidism. Treated in usual manner: high protein diet and thyroxin intravenously. Recovery in one year. Married in August, 1932. Pregnancy and parturition in 1936. Delivery at Jewish Maternity Hospital uneventful. No vestige of original disease. Well to date.

Pregnancy following recovery without sequelae.

Case 9: F. S. Age 23. Married three years; had one normal pregnancy. Onset of edema and intense albuminuria in March, 1930; came under observation in June when diagnosis of chronic nephrosis was made. Treated in usual manner with complete recovery. In 1933 suffered from trichiniasis and a few months later a Neisserian infection with polyarthritis. Complement fixation test positive up to 1936; ankylosis of joints of hand still present. In July, 1936, became pregnant. Normal parturition; delivered at Sloane Maternity Hospital in March, 1937, and is completely well with no vestiges of the original disease today. Survival 7 years.

Recovery followed by trichiniasis, Neisserian infection and pregnancy without renal sequelae.

Case 10: L. B. Age 5½. Case of chronic nephrosis with pneumococcic peritonitis. Operated on because of clinical similarity to acute appendicitis. Came under observation in 1933 in a moribund condition as a result of a complete intestinal obstruction, with uncontrollable fecal vomiting. Patient operated on. Resection of 16 inches of gangrenous small intestine. Open ends of intestine left in the wound. Notwithstanding leakage of intestinal contents patient began to improve. Discharged from hospital six weeks later with intestinal ends still open. Re-operated on three months later; end to end anastomosis. Uneventful surgical recovery. With the improvement in the nutritional state the nephrosis completely subsided. Under treatment eighteen months. In perfect health to date. Survival 6 years.

Nephrosis complicated by pneumococcus peritonitis—intestinal obstruction. Surgical intervention. Recovery from nephrosis.

One cannot reconcile these results with any concept or classification of genuine nephrosis as chronic glomerulonephritis.

To attain these results two tenets must be adhered to: 1. conviction, and 2. persistence.